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(54) Title: TRISUBSTITUTED PHENYL DERIVATIVES AS PHOSPHODIESTERASE INHIBITORS AND PROCESSES FOR THEIR PREPARATION			
(57) Abstract			
<p>Compounds of general formula (1) are described wherein Y is a halogen atom or a group -OR¹, where R¹ is an optionally substituted alkyl group; X is -O-, -S- or -N(R⁷), where R⁷ is a hydrogen atom or an alkyl group; R² is an optionally substituted cycloalkyl or cycloalkenyl group; R³ and R⁴, which may be the same or different, is each a hydrogen atom or an alkyl, -CO₂R⁸ (where R⁸ is a hydrogen atom or an alkyl, aryl, or aralkyl group), -CONR⁹R¹⁰ (where R⁹ and R¹⁰ which may be the same or different is each a hydrogen atom or an alkyl, aryl or aralkyl group), -CSNR⁹R¹⁰, -CN, -CH₂CN group; Z is -(CH₂)_n (where n is zero or an integer 1, 2 or 3; R⁵ is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; R⁶ is a hydrogen atom or a hydroxyl group; and the salts, solvates, hydrates, prodrugs and N-oxides thereof. Compounds according to the invention are potent and selective phosphodiesterase type IV inhibitors and are useful in the prophylaxis and treatment of diseases such as asthma where an unwanted inflammatory response or muscular spasm is present.</p>			
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TRISUBSTITUTED PHENYL DERIVATIVES AS PHOSPHODIESTERASE
INHIBITORS AND PROCESSES FOR THEIR PREPARATION

5

This invention relates to a novel series of tri-substituted phenyl derivatives. to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

10 Many hormones and neurotransmitters modulate tissue function by elevating intra-cellular levels of adenosine 3', 5'-cyclic monophosphate (cAMP). The cellular levels of cAMP are regulated by mechanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenylyl cyclase which may be directly activated by agents such as
15 forskolin or indirectly activated by the binding of specific agonists to cell surface receptors which are coupled to adenylyl cyclase. The breakdown of cAMP is controlled by a family of phosphodiesterase (PDE) isoenzymes, which also control the breakdown of guanosine 3',5'-cyclic monophosphate (cGMP). To date, seven members of the family have
20 been described (PDE I-VII) the distribution of which varies from tissue to tissue. This suggests that specific inhibitors of PDE isoenzymes could achieve differential elevation of cAMP in different tissues, [for reviews of PDE distribution, structure, function and regulation, see Beavo & Reifsnnyder (1990) TIPS, 11: 150-155 and Nicholson et al (1991) TIPS, 12:
25 19-27].

There is clear evidence that elevation of cAMP in inflammatory leukocytes leads to inhibition of their activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect. In these tissues, PDE IV
30 plays a major role in the hydrolysis of cAMP. It can be expected, therefore, that selective inhibitors of PDE IV would have therapeutic effects in inflammatory diseases such as asthma, by achieving both anti-inflammatory and bronchodilator effects.

35 The design of PDE IV inhibitors has met with limited success to date, in that many of the potential PDE IV inhibitors which have been synthesised have lacked potency and/or have been capable of inhibiting more than one type of PDE isoenzyme in a non-selective manner. Lack of a selective

action has been a particular problem given the widespread role of cAMP *in vivo* and what is needed are potent selective PDE IV inhibitors with an inhibitory action against PDE IV and little or no action against other PDE isoenzymes.

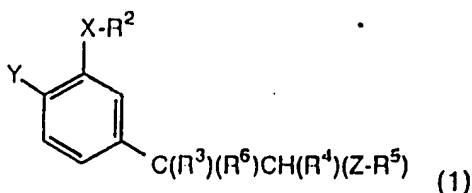
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We have now found a novel series of tri-substituted phenyl derivatives, members of which, compared to known structurally similar compounds, are potent inhibitors of PDE IV at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit the isolated PDE IV enzyme and also elevate cAMP in isolated leukocytes. Certain compounds prevent inflammation in the lungs or pleural cavity induced by carrageenan, platelet-activating factor (PAF), interleukin-5 (IL-5) or antigen challenge. These compounds also suppress the hyperresponsiveness of airway smooth muscle seen in inflamed lungs.

Advantageously, compounds according to the invention have good oral activity and at orally effective doses exhibit little or none of the side-effects associated with known PDE IV inhibitors, such as rolipram. The compounds of the invention are therefore of use in medicine, especially in the prophylaxis and treatment of asthma.

20

Thus according to one aspect of the invention, we provide a compound of formula (1)



25

wherein

Y is a halogen atom or a group -OR¹, where R¹ is an optionally substituted alkyl group;

X is -O-, -S-, or -N(R⁷)-, where R⁷ is a hydrogen atom or an alkyl group;

R² is an optionally substituted cycloalkyl or cycloalkenyl group;

30

R³ and R⁴, which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, -CO₂R⁸ (where R⁸ is a hydrogen atom or an optionally substituted alkyl, aryl or aralkyl group), -CONR⁹R¹⁰ (where R⁹ and R¹⁰ which may be the same or different is as described for R⁸), -CSNR⁹R¹⁰, -CN, or -CH₂CN group;

Z is $-(CH_2)_n-$ where n is zero or an integer 1, 2 or 3;

R⁵ is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

- 5 R⁶ is a hydrogen atom or a hydroxyl group;
and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

10 It will be appreciated that the compounds of formula (1) may have one or more chiral centres, depending on the nature of the groups R³, R⁴, R⁵, R⁶ and Z. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates.

- 15 In the following description, a reference to an alkyl group, whether it is an individual group or part of a larger group, is intended to mean, where possible, a straight or branched alkyl group.

- 20 In the compounds of formula (1), when Y is a halogen atom it may be for example a fluorine, chlorine, bromine or iodine atom.

- 25 When Y in the compounds of formula (1) is a group -OR¹, R¹ may be, for example, an optionally substituted C₁₋₃alkyl group, such as a methyl, ethyl, n-propyl, or i-propyl group. Optional substituents which may be present on R¹ groups include one or more halogen atoms, e.g. fluorine, or chlorine atoms.

- 30 When X in compounds of formula (1) is a -N(R⁷)- group it may be a -NH- group or a group -N(R⁶)- where R⁶ is an optionally substituted C₁₋₆ alkyl group such as a methyl or ethyl group.

- 35 When R² in the compounds of formula (1) is an optionally substituted cycloalkyl or cycloalkenyl group it may be for example a C₃₋₈cycloalkyl group such as a cyclobutyl, cyclopentyl or cyclohexyl group or a C₃₋₈cycloalkenyl group containing for example one or two double bonds such as a 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-

yl or 3,5-cyclohexadien-1-yl group, each cycloalkyl or cycloalkenyl group being optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, straight or branched C₁₋₆alkyl e.g. C₁₋₃alkyl such as methyl or ethyl, hydroxyl or C₁₋₆alkoxy e.g. C₁₋₃alkoxy such as methoxy or ethoxy groups.

Alkyl groups represented by R³ and R⁴ in compounds of formula (1) include C₁₋₆ alkyl groups, for example C₁₋₃ alkyl groups, such as methyl, ethyl, n-propyl or i-propyl groups. Optional substituents which may be present on R³ or R⁴ include one or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C₁₋₆alkoxy e.g. C₁₋₃alkoxy such as methoxy or ethoxy groups, or thiol or C₁₋₆alkylthio e.g. C₁₋₃alkylthio such as methylthio or ethylthio groups.

Particular examples of R³ or R⁴ alkyl groups include -CH₃, -CH₂CH₃, -CH₂OH, -CH₂Cl, -CH₂F, -CHCl₂, -CHF₂ and -CH₂OCH₃ groups.

When R³ and/or R⁴ is a -CO₂R⁸, -CONR⁹R¹⁰ or CSNR⁹R¹⁰ group it may be for example a -CO₂H, -CONH₂, or -CSNH₂ group, or a group -CO₂R⁸, -CONR⁹R¹⁰, -CSNR⁹R¹⁰ -CONHR¹⁰ or -CSNHR¹⁰ wherein R⁸, R⁹ and R¹⁰ where present is a C₁₋₃ alkyl group such as a methyl or ethyl group, a C₆₋₁₂ aryl group, for example an optionally substituted phenyl, or a 1- or 2-naphthyl group, or a C₆₋₁₂ aryl C₁₋₃ alkyl group such as an optionally substituted benzyl or phenethyl group. Optional substituents which may be present on these groups include R¹¹ substituents discussed below in relation to the group R⁵.

In the compounds of formula (1) Z may represent a bond connecting the group R⁵ to the rest of the molecule, or represents a group -CH₂-, -(CH₂)₂- or (CH₂)₃-.

Monocyclic or bicyclic aryl groups represented by the group R⁵ in compounds of formula (1) include for example C₆₋₁₂ optionally substituted aryl groups, for example optionally substituted phenyl, 1- or 2-naphthyl, indenyl or isoindenyl groups.

When the monocyclic or bicyclic aryl group contains one or more heteroatoms it may be a C₁₋₉, for example a C₃₋₉, optionally substituted heteroaryl group containing for example one, two, three or more heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, heteroaryl groups may be for example monocyclic or bicyclic heteroaryl groups. Monocyclic heteroaryl groups include for example five- or six-membered heteroaryl groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Examples of heteroaryl groups represented by Ar include pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl.

The heteroaryl group represented by R⁵ may be attached to the remainder of the molecule of formula (1) through any ring carbon or heteroatom as appropriate. Thus, for example, when the group Ar is a pyridyl group it may be a 2-pyridyl, 3-pyridyl or 4-pyridyl group. When it is a thienyl group it may be a 2-thienyl or 3-thienyl group, and, similarly, when it is a furyl group it may be a 2-furyl or 3-furyl group.

When in compounds of formula (1) the heteroaryl group is a nitrogen-containing heterocycle it may be possible to form quaternary salts, for example N-alkyl quaternary salts and the invention is to be understood to extend to such salts. Thus for example when the group Ar is a pyridyl group, pyridinium salts may be formed, for example N-alkylpyridinium salts such as N-methylpyridinium.

The aryl or heteroaryl groups represented by R⁵ in compounds of formula (1) may each optionally be substituted by one, two, three or more substituents [R¹¹]. The substituent R¹¹ may be selected from an atom or group R¹² or -Alk¹(R¹²)_m wherein R¹² is a halogen atom, or an amino

(-NH₂), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, formyl [HC(O)-], carboxyl (-CO₂H), esterified carboxyl, thiol (-SH), substituted thiol, -C(O)R^{8a} [where R^{8a} is as defined above for R⁸], -SO₃H, -SO₂R^{8a}, -SO₂N(R^{8a})(R^{9a}), (where R^{9a} is as described above for R^{8a} and may be the same as or different to R^{8a} .
 5 -CON(R^{8a})(R^{9a}), -NHSO₂R^{8a}, -N(SO₂R^{8a})₂, -NHSO₂N(R^{8a})(R^{9a}), -NHC(O)R^{8a}, or -NHC(O)OR^{8a} group; Alk¹ is a straight or branched C₁-₆alkylene, C₂-₆alkenylene, or C₂-₆alkynylene chain optionally interrupted by one, two, or three -O-, or -S- atoms or -S(O)_p-, [where p is an integer 1
 10 or 2] or -N(R⁷)- groups; and m is zero or an integer 1, 2 or 3.

When in the group -Alk¹(R¹²)_m m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R¹² may be present on any suitable carbon atom in -Alk¹. Where more than one R¹² substituent is
 15 present these may be the same or different and may be present on the same or different carbon atom in Alk¹. Clearly, when m is zero and no substituent R¹² is present the alkylene, alkenylene or alkynylene chain represented by Alk¹ becomes an alkyl, alkenyl or alkynyl group.

20 When R¹² is a substituted amino group it may be a group -NH[Alk¹(R¹³)_m] [where Alk¹ and m are as defined above and R^{13a} is as defined above for R¹² but is not a substituted amino, a substituted hydroxyl or a substituted thiol group] or a group -N[Alk¹(R¹³)_m]₂ wherein each -Alk¹(R¹³)_m group is the same or different.

25 When R¹² is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R¹² is a cycloalkoxy group it may be for example a C₅-₇cycloalkoxy group such as a cyclopentyloxy or cyclohexyloxy group.
 30

When R¹² is a substituted hydroxyl or substituted thiol group it may be a group -OAlk¹(R¹³)_m or -SAlk¹(R¹³)_m respectively, where Alk¹, R¹³ and m are as just defined.

35 Esterified carboxyl groups represented by the group R¹² include groups of formula -CO₂Alk² wherein Alk² is a straight or branched, optionally

substituted C₁₋₈alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C₆₋₁₂arylC₁₋₈alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C₆₋₁₂aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₂aryloxyC₁₋₈alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C₆₋₁₂aroyloxyC₁₋₈alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk² group include R¹¹ substituents described above.

When Alk¹ is present in or as a substituent R¹¹ it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butyneylene or 3-butyneylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R⁷)- groups.

Particularly useful atoms or groups represented by R¹¹ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl or ethyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆ hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C₁₋₆alkylthiol e.g. methylthiol or ethylthiol, C₁₋₆alkoxy, e.g. methoxy or ethoxy, C₅₋₇cycloalkoxy, e.g. cyclo-pentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk² [where Alk² is as defined above], C₁₋₆alkanoyl e.g. acetyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, arylaminosulphonyl, e.g. optionally substituted phenylaminosulphonyl, aralkylaminosulphonyl, e.g. optionally substituted benzylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethyl-

aminocarbonyl or diethylaminocarbonyl, sulphonylamino (-NHSO₂H), C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylamino-
5 sulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, C₁₋₆alkanoylamino C₁₋₆alkyl, e.g. acetylaminomethyl or C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonyl-
10 amino or t-butoxycarbonylamino groups.

Where desired, two R¹¹ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₂₋₆alkylenedioxy group such as ethylenedioxy.

15

It will be appreciated that where two or more R¹¹ substituents are present, these need not necessarily be the same atoms and/or groups. The R¹¹ substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in
20 phenyl groups represented by R⁵ any substituent may be present at the 2-, 3-, 4-, 5- or 6- positions relative to the ring carbon atom attached to the remainder of the molecule.

In the compounds of formula (1), when an ester group is present, for
25 example a group -CO₂Alk² this may advantageously be a metabolically labile ester.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include
30 pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides,
35 alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or

aminocarbonyl or diethylaminocarbonyl, sulphonylamino ($-\text{NHSO}_2\text{H}$), C_{1-6} alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6} dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino ($-\text{NHSO}_2\text{NH}_2$), C_{1-6} alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6} dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6} alkanoylamino, e.g. acetylamino, C_{1-6} alkanoylamino C_{1-6} alkyl, e.g. acetylaminomethyl or C_{1-6} alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino groups.

Where desired, two R^{11} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{2-6} alkylenedioxy group such as ethylenedioxy.

It will be appreciated that where two or more R^{11} substituents are present, these need not necessarily be the same atoms and/or groups. The R^{11} substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups represented by R^5 any substituent may be present at the 2-, 3-, 4-, 5- or 6- positions relative to the ring carbon atom attached to the remainder of the molecule.

In the compounds of formula (1), when an ester group is present, for example a group $-\text{CO}_2\text{Alk}^2$ this may advantageously be a metabolically labile ester.

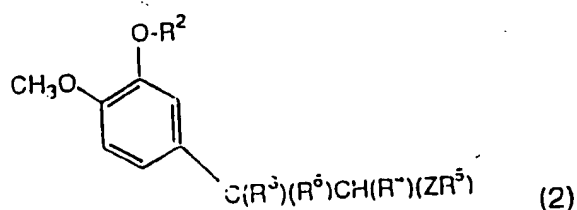
The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or

napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

- 5 Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.
- 10 Prodrugs of compounds of formula (1) include those compounds, for example esters, alcohols or aminos, which are convertible in vivo by metabolic means, e.g. by hydrolysis, reduction, oxidation or transesterification, to compounds of formula (1).
- 15 Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.
- 20 In the compounds of formula (1), the group Y is preferably an -OR¹ group, especially where R¹ is an optionally substituted ethyl group or, especially, an optionally substituted methyl group. Especially useful substituents which may be present on R¹ groups include one, two or three fluorine or chlorine atoms.
- 25 The group X in compounds of formula (1) is preferably -O-.

A particularly useful group of compounds of formula (1) has the formula (2):



5 where R^2 is an optionally substituted cycloalkyl group; R^3 , R^4 , R^5 , R^6 and Z are as defined for formula (1); and the salts, solvates, hydrates and N-oxides thereof.

In the compounds of formulae (1) and (2) R^2 is preferably an optionally substituted cyclopentyl group. In particular, R^2 is a cyclopentyl group.

10

The group R^3 in compounds of formulae (1) or (2) is preferably a hydrogen atom or a C_{1-3} alkyl group, particularly a methyl group.

15 In compounds of formulae (1) or (2) the group R^4 is preferably a hydrogen atom or a -CN or optionally substituted C_{1-3} alkyl, especially a - CH_3 group.

20 Z in the compounds of formulae (1) or (2) is preferably $-(CH_2)_n-$ where n is zero, 1 or 2. In particular, however, Z is especially $-(CH_2)_n-$ where n is zero.

25 R^5 in the compounds of formulae (1) or (2) is preferably an optionally substituted phenyl group, particularly a phenyl group optionally substituted by one, two or more R^{11} groups, and is especially a 2- or 3-monosubstituted or 2,6-disubstituted phenyl group. Particular substituents include halogen atoms, especially fluorine or chlorine atoms, and nitro, amino, alkoxy, haloalkyl, hydroxy, $-NHCOR^{8a}$, $-NHCONHR^{8a}$ and $-NHSO_2R^{8a}$ groups.

30 Particular R^5 groups include 2-nitrophenyl, 2-aminophenyl 2-haloalkylphenyl, e.g. 2-trifluoroalkylphenyl, 2-halophenyl, e.g. 2-fluorophenyl, 2-chlorophenyl, or 2-bromophenyl, 3-halophenyl, e.g. 3-fluorophenyl, 2,6-dihalophenyl, e.g. 2,6-difluorophenyl, or 2,6-dichlorophenyl, and 2, 6-dialkoxyphenyl, e.g. 2, 6-dimethoxyphenyl.

35

Other particularly useful R^5 groups in compounds of formulae (1) and (2) include 2,3- and 4-pyridinyl, thienyl, e.g. 2-thienyl or pyrimidinyl, especially 2-pyrimidinyl, groups, optionally substituted by one, two or more

R¹¹ groups, especially halogen atoms, e.g. fluorine or chlorine atoms, nitro, amino, alkoxy, haloalkyl, hydroxy, -NHCOR^{8a}, -NHCONHR^{8a} or -NHSO₂R^{8a} groups.

- 5 Particularly useful groups of compounds of formulae (1) or (2) are those wherein R³ is a hydrogen atom or a methyl group, R⁴ is a hydrogen atom or a -CN or -CH₃ group and Z is a bond, and the salts, solvents, hydrates and N-oxides thereof. Especially useful compounds in groups of these types are those wherein R⁵ is an optionally substituted phenyl, pyrimidinyl or pyridyl, e.g. 3- or 4- pyridyl, group. Particularly useful pyridyl groups of
10 these types are 3,5-disubstituted-4-pyridyl and 3-monosubstituted -4-pyridyl.

R⁶ in compounds of formula (1) or (2) is preferably a hydrogen atom.

15

Particularly useful compounds according to the invention are:

- 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;
3-Amino-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;
20 N-[4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-3-pyridyl]phenyl-sulphonamide
(±)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)propanenitrile;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-3,5-dichloropyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-3-isobutylamidopyridine;
25 3-(3-Benzylureido)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;
or
3-Benzamido-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;
and the salts, solvates, hydrates and N-oxides thereof.

- 30 Compounds according to the invention are selective and potent orally active inhibitors of PDE IV. The ability of the compounds to act in this way may be simply determined by the tests described in the Examples hereinafter.

- 35 The compounds according to the invention are thus of particular use in the prophylaxis and treatment of human or animal diseases where an unwanted inflammatory response or muscular spasm (for example bladder

or alimentary smooth muscle spasm) is present and where the elevation of cAMP levels may be expected to prevent or alleviate the inflammation and relax muscle.

5 Particular uses to which the compounds of the invention may be put include the prophylaxis and treatment of asthma, especially inflamed lung associated with asthma, cystic fibrosis, or in the treatment of inflammatory
10 airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and atherosclerosis.

15 Compounds of the invention also suppress neurogenic inflammation through elevation of cAMP in sensory neurones. They are, therefore, analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

20 Compounds according to the invention may also elevate cAMP in lymphocytes and thereby suppress unwanted lymphocyte activation in immune-based diseases such as rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease.

25 Compounds according to the invention have also been found to reduce gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion.

30 Compounds of the invention suppress cytokine synthesis by inflammatory cells in response to immune or infectious stimulation. They are, therefore, useful in the treatment of bacterial, fungal or viral induced sepsis and septic shock in which cytokines such as tumour necrosis factor (TNF) are key mediators. Also compounds of the invention suppress inflammation
35 and pyrexia due to cytokines and are, therefore, useful in the treatment of inflammation and cytokine-mediated chronic tissue degeneration which occurs in diseases such as rheumatoid or osteo-arthritis.

Over-production of cytokines such as TNF in bacterial, fungal or viral infections or in diseases such as cancer, leads to cachexia and muscle wasting. Compounds of the invention ameliorate these symptoms with a consequent enhancement of quality of life.

5

Compounds of the invention also elevate cAMP in certain areas of the brain and thereby counteract depression and memory impairment.

10

Compounds of the invention suppress cell proliferation in certain tumour cells and can be used, therefore, to prevent tumour growth and invasion of normal tissues.

15

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

20

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation. Forms suitable for oral administration are particularly useful.

25

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution

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with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous

vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

- 5 Preparations for oral administration may be suitably formulated for adult or pediatric use and/or to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

- 10 The compounds of formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or
15 aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

- 20 In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

- 25 For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other
30 suitable gas or mixture of gases.

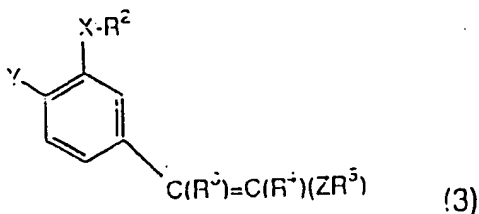
- The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by
35 instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular inflammatory condition will vary depending on the

compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg, e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds according to the invention may be prepared by the following processes. The symbols Y, R², R³, R⁴, R⁵, R⁶, R⁷ and X, when used in the formulae below are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio, or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis" John Wiley and Sons, 1981.] It may be that deprotection will form the last step in the synthesis of compounds of formula (1). Thus, in one example, compounds of formula (1) wherein R⁴ and/or R⁵ contains a carboxylic acid group may be prepared by deprotecting the corresponding compound wherein R⁴ and/or R⁵ contains a protected carboxyl group, such as an oxazolinyll group, e.g. 4,4-dimethyl-2-oxazolinyll, in the presence of a base, e.g. sodium hydroxide, in an acid solvent e.g. aqueous hydrochloric acid, at an elevated temperature, e.g. the reflux temperature.

Thus according to a further aspect of the invention a compound of formula (1) wherein R³ is as defined for formula (3) but is not a -CN or -CH₂CN group and R⁶ is a hydrogen atom may be prepared by hydrogenation of a compound of formula (3):

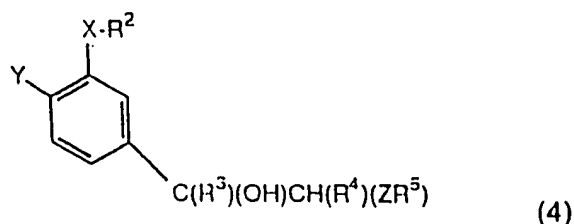


using for example hydrogen in the presence of a metal.

Suitable metals include for example platinum or palladium, optionally supported on an inert carrier such as carbon or calcium carbonate. The reaction may be performed in a suitable solvent, for example an alcohol such as ethanol or an ether such as tetrahydrofuran, optionally in the presence of a base, for example a tertiary organic base such as triethylamine, at for example ambient temperature.

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Intermediates of formula (3) may be prepared by dehydration of an alcohol of formula (4).



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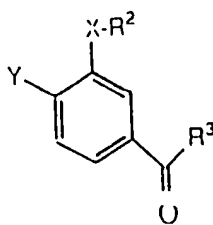
using an acid at an elevated temperature.

Suitable acids include for example phosphoric or sulphonic acids, e.g. 4-toluenesulphonic acid. The reaction may be performed in an inert organic solvent, for example a hydrocarbon such as toluene, at an elevated temperature, for example the reflux temperature.

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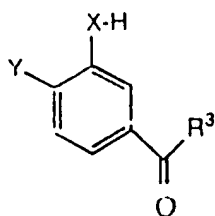
It will be appreciated that alcohols of formula (4) are compounds of the invention in which the group R^6 is a hydroxyl group. Thus according to a further aspect of the invention, a compound of formula (1) wherein R^6 is a hydroxyl group and R^3 is as defined for formula (1) but is not a $-CN$ or $-CH_2CN$ group may be prepared by reaction of a ketone or aldehyde of formula (5)

25



(5)

- 5 with an organometallic reagent R^4R^5ZCHM [where M is a metal atom, for example a lithium atom] in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, at a low temperature e.g. around -70°C to ambient temperature.
- 10 Reagents R^4R^5ZCHM are either known compounds or may be prepared, preferably in situ during the above process, by reaction of a compound AlkCH_2M or $[\text{Alk}]_2\text{NM}$ [where Alk is an alkyl group such as a n-propyl or i-propyl group] with a compound $R^4R^5ZCH_2$ using the just mentioned reaction conditions.
- 15 Intermediates of formula (5) may be prepared by alkylation of a corresponding compound of formula (6)

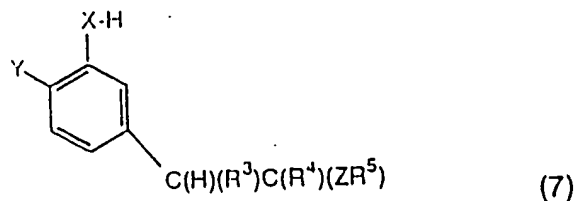


(6)

- 20 using a compound $R^2\text{Hal}$ [where Hal is a halogen atom such as a bromine or chlorine atom] where necessary in the presence of a base such as caesium or potassium carbonate or an alkoxide such as potassium t-butoxide, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide at ambient temperature or above e.g. around 40°C to 50°C .
- 25 Intermediates of formula (5) are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.

According to a still further aspect of the invention a compound of formula (1) wherein R^6 is a hydrogen atom may be prepared by alkylation of a compound of formula (7)

5



with a halide $R^2\text{Hal}$, or with an alcohol $R^2\text{OH}$.

- 10, The alkylation with the halide $R^2\text{Hal}$ may be performed using the reagents and conditions described above for the preparation of compounds of formula (6). Alkylation using an alcohol $R^2\text{OH}$ may be performed in the presence of a phosphine, such as triphenylphosphine, and an activator, for example diethyl azodicarboxylate, in the presence of an organic base such as triethylamine in a solvent such as tetrahydrofuran at an elevated temperature, e.g. the reflux temperature [see for example Mitsunobu, O., Synthesis, 1981, 1].

- 20 Intermediates of formula (7) may be prepared by reaction of an aldehyde or ketone of formula (6) with a compound $R^5\text{ZCH}_2\text{R}^4$ in the presence of a base or an acid in a suitable solvent.

- 25 Bases for use in this reaction include inorganic bases, for example alkali and alkaline earth metal bases, e.g. hydroxides, such as sodium or potassium hydroxide; alkoxides, for example sodium ethoxide, and organic bases, for example amines such as piperidine. Suitable solvents include alcohols such as ethanol. Acids for use in the reaction include organic acids, e.g. carboxylic acids such as acetic acid.

- 30 The reaction may be performed at any suitable temperature, for example from around ambient temperature to the reflux temperature depending on the nature of the starting materials.

In general, the base, acid, solvent and reaction conditions may be selected depending on the nature or the starting materials, from a range of known alternatives for reactions of this type.

- 5 In this reaction the group X-H may need to be in a protected state. Conventional hydroxy, amino or thiol protecting groups may be used in accordance with standard practice [see, for example, Green T. W., in "Protective Groups in Organic Synthesis" John Wiley and Sons, 1981].
- 10 Where an intermediate of formula (7) in which R^3 is a $-CN$ or $-CH_2CN$ group is required this may be prepared by interconversion of a corresponding compound in which R^3 is $-CONH_2$ or $-CH_2CONH_2$ as discussed below in relation to compounds of formula (1). Intermediates $R^5ZCH_2R^4$ are either known compounds or may be prepared from known
- 15 starting materials by methods analogous to those used for the preparation of the known compounds.

- Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1). Thus, for example, a substituted
- 20 monocyclic or bicyclic aryl group R^5 in compounds of formula (1) may be generally obtained by an appropriate substitution reaction using the corresponding unsubstituted compound of formula (1) and a R^{12} containing nucleophile or electrophile. In another general process, a group R^3 and/or R^4 in formula (1) may be manipulated using conventional
- 25 chemical procedures to yield other groups R^3 and/or R^4 .

- Thus in one example of an interconversion process a compound of formula (1) wherein R^5 contains a $-CH_2NH_2$ substituent may be prepared by reduction of a corresponding compound wherein R^5 contains a nitrile
- 30 group, using for example a complex metal hydride such as lithium aluminium hydride in a solvent such as an ether e.g. diethylether.

- In a further example, a compound of formula (1) wherein R^5 contains a $-NHCOR^{8a}$, $-NHCONHR^{8a}$, $-NHCON(R^{8a})_2$, $-NHCSR^{8a}$ or alkanoyl-
- 35 aminoalkyl substituent may be prepared by acylation or thiolation of a corresponding compound wherein R^5 contains a $-NH_2$ or alkylamino group by reaction with an acyl halide e.g. an acyl chloride, an alkyl or aryl isocyanate, or a thiol halide in the presence of a base, such as a tertiary

amine e.g. triethylamine or pyridine, optionally in a solvent such as dichloromethane.

5 in a still further example, a compound of formula (1) wherein R⁵ contains an alkoxy substituent may be prepared by alkylation of a corresponding compound wherein R⁵ contains a hydroxyl group by reaction with a compound AlkHal [where Alk is a C₁₋₆ alkyl group such as a methyl or ethyl group and Hal is a halogen atom such as an iodine atom] in the presence of a base such as caesium or potassium carbonate in a dipolar aprotic solvent such as an amide, e.g. dimethylformamide at ambient temperature or above.

15 In another example a compound of formula (1) wherein R³ and/or R⁴ is a -CN or -CH₂CN group may be prepared by dehydration of a corresponding amide where R³ and/or R⁴ is -CONH₂ or -CH₂CONH₂ using for example trifluoroacetic anhydride in the presence of a base such as pyridine in a solvent such as tetrahydrofuran.

20 N-oxides of compounds of formula (1) may be prepared by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C.

25 Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent using conventional procedures.

30 Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers. Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of the mixture of enantiomers of formula (1) and an appropriate chiral compound e.g. a chiral acid or base. The diastereomers may then be separated by any convenient means for example by crystallisation and the desired enantiomer recovered, e.g. by 35 treatment with an acid or base in the instance where the diastereomer is a

salt. In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography.

The following examples illustrate the invention.

5

The following abbreviations are used:

DMF	dimethylformamide
THF	tetrahydrofuran
DME	dimethoxyethane
10 EIOAc	ethyl acetate
Et ₂ O	diethylether
RT	room temperature
LDA	lithium diisopropylamide

15

INTERMEDIATE 1

3-Cyclopentyloxy-4-methoxybenzaldehyde

Caesium carbonate (214g, 0.66mol) was added to a mixture of 3-hydroxy-4-methoxybenzaldehyde (100g, 0.66mol) and cyclopentyl bromide (98g, 0.66mol) in anhydrous DMF (50ml). The reaction mixture was stirred at 20 RT for 16h then treated with a further portion of cyclopentyl bromide (98g, 0.66mol) and caesium carbonate (214g, 0.66mol). After a further 6h at RT, the mixture was filtered and concentrated in vacuo. The residue was dissolved in dichloromethane (300ml) and washed with sodium hydroxide 25 solution (10%; 2x150ml). The organic layer was dried (MgSO₄), concentrated in vacuo, and distilled (150°C, 10⁻²mbar) to afford the title compound (130g) as a viscous colourless oil. (Found: C, 70.38; H, 7.48. C₁₃H₁₆O₃ requires C, 70.89; H, 7.32%); δ H (CDCl₃) 1.5-2.0 (8H, br m, CH₂)₄), 3.87 (3H, s, OMe), 4.80 (1H, br m, OCHCH₂), 6.90 (1H, d, \downarrow 30 8.7Hz, ArH ortho to OMe), 7.30-7.45 (2H, m, 2xArH meta to OMe), and 9.77 (1H, s, ArCHO).

INTERMEDIATE 2

3,5-Dichloro-4-methylpyridine

35 3,5-Dichloropyridine (2.04g, 13.5mmol) in THF (5ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (1.9ml, 13.5mmol) and n-butyllithium (1.6M, 8.4ml, 13.5mmol)] in THF (25ml) at -70°C. After stirring at this temperature for 5 min. iodomethane (0.85ml, 13.5 mmol)

was added and the reaction mixture stirred for a further 1.5h at -70°C. Saturated sodium hydrogen carbonate solution (20ml) and dichloromethane (20ml) was added and the organic phase separated, dried (MgSO₄), and concentrated in vacuo. The residue was subjected to chromatography (SiO₂; Et₂O-hexane, 1:3) to afford the title compound (1.16g) as a pale yellow solid. δ_H (CDCl₃) 2.46 (3H, s, Me), and 8.36 (2H, s, pyridine H₂, H₆).

INTERMEDIATE 3

10 a) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-pyridyl) propenenitrile

2-Pyridylacetonitrile (1.23g, 11mmol) and Intermediate 1 (2.20g, 10mmol) were dissolved in ethanol (3ml) and added to a solution of sodium hydroxide (0.5g) in water (4.5ml). The reaction mixture was allowed to stir at RT for 2h then partitioned between dichloromethane (20ml) and saturated sodium hydrogen carbonate solution (15ml). The organic layer was separated, dried (MgSO₄), and concentrated in vacuo to give the crude product. Trituration of the crude product with ethanol gave the title compound (2.40g) as a yellow solid m.p. 82.5-83°C (Found: C, 78.87; H, 6.27; N, 8.46. C₂₀H₂₀N₂O₂ requires C, 74.98; H, 6.29; N, 8.74%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.824 (3H, s, OMe), 4.80 (1H, br m, OCHCH₂), 6.84 (1H, d, \downarrow 8.6Hz, ArH ortho to OMe), 7.05-7.25 (1H, m, pyridine H₅), (1H, dd, \downarrow 8.6, 1.95Hz, ArH para to OMe), 7.6-7.75 (3H, m, ArH ortho to cyclopentyloxy + pyridine H₃, H₄), 8.29 (1H, s, CH=CCN) and 8.52 (1H, ca.d, \downarrow 4.6 Hz, pyridine H₆); m/z 320 (M⁺, 15%), 252 (38), 251 (100), 237 (5), 236 (10), 209 (5), 179 (5), and 41 (8).

b) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-pyridyl) propenenitrile

30 Prepared in a similar manner to Intermediate 3 a) using 3-pyridylacetonitrile (2.35ml, 22mmol) and Intermediate 1 (4.40g, 20mmol). Chromatography (SiO₂; EtOAc) gave the title compound (5.31g) as a pale yellow solid m.p. 86.5-87.5°C (Found: C, 74.80; H, 6.26; N, 8.74. C₂₀H₂₀N₂O₂ requires C, 74.98; H, 6.29; N, 8.74%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.87 (3H, s, OMe), 4.82 (1H, br m, OCHCH₂), 6.86 (1H, d, \downarrow 8.6Hz, ArH ortho to OMe), 7.2-7.4 (2H, m, ArH para to OMe + pyridine H₃), 7.42 (1H, s, CH=CCN), 7.70 (1H, d, \downarrow 2.0Hz, ArH ortho to cyclopentyloxy), 7.87 (1H, dm, \downarrow 7.6Hz, pyridine H₄), 8.53 (1H, dd, \downarrow 4.8,

1.3Hz, pyridine H_6) and 8.84 (1H, d, J 2.4Hz, pyridine H_2); m/z 320 (M^+ , 20%), 252 (100), 251 (67), 234 (20), 223 (27), 205 (27), 151 (50), 69 (22), and 41 (31).

5 c) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)propenenitrile

Prepared in a similar manner to Intermediate 3 c) using 4-pyridylacetonitrile (1.7g, 11mmol) and Intermediate 1 (2.20g, 20mmol). Trituration of the crude product with ethanol gave the title compound (2.75g) as an orange solid m.p. 125-127°C. (Found: C, 74.84; H, 6.29; N, 8.33. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.84 (3H, s, OMe), 4.83 (1H, br m, $OCHCH_2$), 6.83 (1H, d, J 8.2Hz, ArH ortho to OMe), 7.26 (1H, dd, J 8.2, 2.2Hz, ArH para to OMe), 7.44 (2H, dd, J 4.7, 1.7Hz pyridine H_3, H_5), 7.53 (1H, s, $CH=CCN$) 7.69 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy), 8.56 (2H, dd, J 4.7, 1.5 Hz, pyridine H_2, H_6); m/z 320 (M^+ , 28), 253 (19), 252 (100), 251 (59), 224 (15), 223 (38), 209 (10), and 41 (23).

20 d) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-naphthyl)propenenitrile

From 2-naphthylacetonitrile (1.67g, 10mmol) and Intermediate 1 (2.2g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (3.14g) as a pale yellow solid. m.p. 147-148°C (Found: C, 81.15; H, 6.24; N, 3.56. $C_{25}H_{23}NO_2$ requires C, 81.27; H, 6.27; N, 3.79%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.87 (1H, br m, $OCHCH_2$), 6.86 (1H, d, J 8.3Hz, ArH meta to OMe), and 7.2-8.1 (10H, m, 2xArH meta to OMe + $CH=CCN$ + $C_{10}H_7$); m/z 370 (M^+ + 1, 10%), 369 (M^+ , 40), 302 (23), 301 (100), 240 (20), 167 (12), 124 (38), and 41 (10).

30

INTERMEDIATE 4

(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3-nitropyridine

A mixture of Intermediate 1 (2.13g, 9.68mmol), 4-methyl-3-nitropyridine (2.47g, 17mmol), and ammonium acetate (1.19g, 15mmol) in acetic acid (20ml) was heated to reflux for 3h. The reaction mixture was cooled and partitioned between dichloromethane (20ml) and saturated sodium hydrogen carbonate solution (2 x 10ml). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to

chromatography (SiO₂; Et₂O-hexane, 1:1) to afford the title compound (1.83g) as an orange solid m.p. 114-116°C. (Found: C, 56.94; H, 5.94; N, 8.01. C₁₉H₂₀N₂O₃ requires C, 67.05; H, 5.92; N, 8.23%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.86 (3H, s, OMe), 4.75 (1H, br m, OCHCH₂), 6.84 (1H, d, J 8.5Hz, ArH ortho to OMe), 7.0-7.2 (2H, m, 2x ArH meta to OMe), 7.30 (1H, s, CH=CH), 7.38 (1H, s, CH=CH), 7.61 (1H, d, J 5.4 Hz, pyridine H₅), 8.73. (1H, d, J 5.4 Hz, pyridine H₆), and 9.09 (1H, s, pyridine H₂); m/z 340 (M⁺, 15%) 308 (25), 240 (69), 226 (20), 225 (34), 152 (100), 151 (31), 149 (29), 121 (29), 68 (26), 67 (66), and 57 (22).

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INTERMEDIATE 5

a) (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3,5-dichloropyridine

The compound of Example 1a) (2.65g, 6.92mmol) was dissolved in toluene (60ml) containing p-toluenesulphonic acid (0.2g) and the mixture heated to reflux for 2.5h in a Dean-Stark apparatus. The reaction mixture was concentrated in vacuo and the residue subjected to chromatography (SiO₂; Et₂O-hexane, 1:2) to afford the title compound (1.55g) as yellow crystals m.p. 99-101°C. (Found: C, 62.68; H, 5.22; N, 3.70. C₁₉H₁₉Cl₂NO₂ requires C, 62.65; H, 5.26; N, 3.85%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.86 (3H, s, OMe), 4.82 (1H, br m, OCHCH₂), 6.83 (1H, d, J 8.9Hz, ArH ortho to OMe), 6.90 (1H, d, J 16.6 Hz, CH=CH) 7.0-7.2 (2H, m, 2x ArH meta to OMe) 7.40 (1H, d, J 16.6 Hz, CH=CH), and 8.42(2H, s, pyridine H₂, H₆); m/z 365 (15%), 363 (20), 297 (67), 296 (28), 295 (100), 262 (29), 260 (79), 245 (36), 230 (22), 228 (27), 216 (23), and 152 (24).

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b) (E)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine

From the compound of Example 1b). The crude product was subjected to chromatography (SiO₂; Et₂O-hexane, 2:1) to afford the title compound (1.58g) as a pale yellow solid m.p. 76-77.5°C. (Found: C, 77.20; H, 7.20; N, 4.63. C₁₉H₂₁NO₂ requires C, 77.26; H, 7.17; N, 4.74%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.84 (3H, s, OMe), 4.80 (1H, br m, OCH), 6.80 (1H, d, J 8.5Hz, ArH ortho to OMe), 6.95 (1H, d, J 15.6 Hz, CH=CH), 6.95-7.7 (5H, m, 2x ArH meta to OMe + pyridine H₃, H₄, H₅), 7.51 (1H, d, J

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1656 Hz, CH=CH), and 8.53 (1H, dm, \downarrow 4.9 Hz, pyridine H₆); m/z 295 (M⁺, 23%), 294 (11), 227 (21), 226 (100), 211 (18), 184 (10), and 154 (13).

c) (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-1-propenyl]pyridine

From Intermediate 8 (1g) Chromatography (SiO₂; dichloromethane) followed by recrystallisation (hexane) afforded a mixture of (Z)- title compound, 4-[2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)propenyl]pyridine, and the title compound (247mg) as white needles m.p. 78-79°C. Found C, 77.64; H, 7.58; N, 4.41 C₂₀H₂₃NO₂ requires C, 77.63; H, 7.49; N, 4.52%. δ_H (80 MHz; CDCl₃) 1.6-2.0 (8H, br m, (CH₂)₄), 2.26 (3H, d, \downarrow 1.3 Hz, CH₃), 3.85 (3H, s, OMe), 4.75-4.85 (1H, m, OCHCH₂), 6.60-7.21 (6H, m, ArH + PyH₃, H₅ + C=CH), and 8.52 (2H, br d, PyH₂, H₆). m/z (EI) 309 (M⁺, 30%), 241 (100), 222 (21), and 212 (29).

d) (E)-3[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-2-methoxy-pyrazine

From Example 2d (3.9g). Chromatography (SiO₂; Et₂O-hexane, 1:1) followed by recrystallisation (i-propanol-hexane, 1:1) afforded the title compound (3.24g) as a yellow solid m.p. 71.73°C.

INTERMEDIATE 6

a) (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridazine

The compound of Example 2a) was dissolved in toluene (50ml) containing 4-toluenesulphonic acid (0.1g) and the mixture heated to reflux in a Dean-Stark apparatus for 2h. The cooled reaction mixture was poured into saturated sodium hydrogen carbonate solution (25ml) and extracted with dichloromethane (1x50ml, 1x25ml). The organic extract was dried (MgSO₄), concentrated in vacuo and the residue subjected to chromatography (SiO₂; Et₂O-hexane, 1:1) to afford the title compound (370mg) (Found: C, 72.75; H, 6.78; N, 9.23. C₁₈H₂₀N₂O₂ requires C, 72.95; H, 6.80; N, 9.45%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.85 (3H, s, OMe), 4.82 (1H, br m, OCH), 6.75-7.7 (7H, br m, ArH ortho to OMe + 2x ArH meta to OMe + CH=CH + pyridazine H₃, H₅), 8.95 (1H, dd, \downarrow 4.3, 1.4 Hz, pyridazine H₆).

b) (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine

Prepared in a similar manner to Intermediate 6a) using the compound of Example 2b). The crude product was subjected to chromatography (SiO₂; EtOAc) to afford the title compound (7.47g) as pale yellow needles m.p. 108-108.5°C (from Et₂O-hexane). (Found: C, 76.92; H, 7.12; N, 4.88. C₁₉H₂₁NO₂ requires C, 77.26; H, 7.17; N, 4.74%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.84 (3H, s, OMe), 4.81 (1H, br m, OCHCH₂), 6.77 (1H, d, \downarrow 15.8 Hz, CH=CH), 6.81 (1H, d, \downarrow ca. 9 Hz, ArH ortho to OMe), 6.95-7.1 (3H, m, ArH meta to OMe + CH=CH), 7.28 (2H, dd, \downarrow 4.7, 1.6 Hz, pyridine H₃, H₅), and 8.49 (2H, dd, \downarrow 4.7, 1.6 Hz, pyridine H₂, H₆); m/z 295 (M⁺, 35%), 228 (20), 227 (100), 226 (86), 198 (34), 184 (23), 167 (12), 166 (16), 154 (10), and 41 (20).

c) (E)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyrazine

Prepared in a similar manner to Intermediate 6a) using the compound of Example 2c). The crude product was subjected to chromatography (SiO₂; ether-hexane, 1:1) to afford the title compound (0.80g) as a pale brown solid m.p. 81-83°C. (Found: C, 72.94; H, 6.78; N, 9.23. C₁₈H₂₀N₂O₂ requires C, 72.94; H, 6.80; N, 9.45%); δ_H (CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 3.84 (3H, s, OMe), 4.80 (1H, br m, OCH), 6.81 (1H, d, \downarrow 8.8 Hz, ArH ortho to OMe), 6.93 (1H, d, \downarrow 15.9 Hz, CH=CH), 7.0-7.15 (2H, m, 2xArH meta to OMe) 7.63 (1H, d, \downarrow 15.9 Hz, CH=CH), and 8.25-8.60 (3H, m, pyrazine H₃, H₅, H₆).

INTERMEDIATE 7

25 (3-Cyclopentyloxy-4-methoxy)phenyl methyl ketone

To a solution of methylmagnesiumbromide (5.44ml) in THF (150ml) at 10°C was added Intermediate 1. The reaction mixture was left to stir at RT for 5-6hr, then NH₄Cl and Et₂O (100ml) were added and the solution stirred for another 90 min (the solution went from hazy to clear). The layers were separated, the aqueous layer was extracted with Et₂O (50ml) the combined organic layer was extracted with a saturated bicarbonate solution (100ml) then brine (100ml). Evaporation in vacuo afforded 1-methoxy-2-cyclopentyloxy-4-(1-hydroxyethyl)benzene which was dissolved in dichloromethane (300ml) before adding MnO₂ (10eq). The reaction mixture was stirred for 120h, then the MnO₂ was filtered off and the solvent evaporation in vacuo. Purification by column chromatography (SiO₂; dichloromethane-hexane, 350-150 to dichloromethane) afforded the title compound.

INTERMEDIATE 8**4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-methyl-2-hydroxyethyl]pyridine**

- 5 To a cold (-78°C) solution of 4-picoline (0.80ml) in THF was added n-BuLi (5.6ml), the solution stirred for 30min then transferred to a cold suspension of cerium chloride anhydrous (2.0g) at -78°C. The reaction mixture was stirred for 1h before adding Intermediate 7 in THF then left to warm to RT overnight. 10% NH₄Cl solution and EtOAc were added, the solution was
- 10 filtered through Celite, washed with EtOAc (150ml) and the organic layer was separated, washed with brine (100ml) then dried (Na₂SO₄). The solvents were evaporated *in vacuo* to afford the title compound (2.367g) as pale off-white crystals m.p. 99-101°C. Found C, 73.21; H, 7.63; N, 4.20. C₂₀H₂₅NO₃ requires C 73.37; H, 7.70; N, 4.28%. *m/z* (EI) 327
- 15 (*M*⁺, 3%), 235 (18), 166 (38), 151 (100), and 93 (54).

EXAMPLE 1**a) (±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]-3,5-dichloropyridine**

- 20 Intermediate 2 (2.22g, 13 mmol) in THF (40ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (2.4ml, 17mmol) and n-butyllithium (1.6M, 10.2ml, 16mmol)] in THF (50ml) at -70°C and the mixture stirred at this temperature for 0.25h. A solution of Intermediate 1 (3.32g, 15mmol) in THF (50ml) was then added at -70°C and the reaction
- 25 mixture allowed to warm to RT overnight. Saturated ammonium chloride solution (50 ml) and dichloromethane (50ml) was added and the organic phase separated, dried (MgSO₄), and concentrated *in vacuo*. The residual yellow solid was triturated with hot Et₂O to afford the title compound (2.65g) as a white solid m.p. 139-140°C (Found: C, 59.49; H, 5.68; N, 3.57. C₁₉H₂₁Cl₂NO₃ requires C, 59.69; H, 5.53; N, 3.66%); δH
- 30 (CDCl₃) 1.5-2.1 (8H, br m, CH₂)₄, 3.81 (3H, s, OMe), 4.7 (1H, br m, OCHCH₂), 5.01 (1H, dd *J* 5.8, 8.4Hz, CHOH), 6.75-6.9 (3H, m, ArH *ortho* to OMe + 2xArH *meta* to OMe), and 8.36 (2H, s, pyridine H₂, H₆); *m/z* 383
- 35 (17), 125 (27), 93 (48), 65 (25), and 41 (34).

The following compounds were prepared in a similar manner to the compound of Example 1a.

b) (±)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]
pyridine

From 2-methylpyridine (1.02g, 11mmol), LDA (1.0equiv), and Intermediate
1 (2.45g, 11mmol). The crude product was subjected to chromatography
(SiO₂; Et₂O) to afford the title compound (2.67g) as a yellow solid m.p. 94-
96°C (Found: C, 72.89; H, 7.43; N, 4.58. C₁₉H₂₃NO₃ requires C, 72.82;
H, 7.40; N, 4.47%); δ_H (CDCl₃) 1.5-2.1 (9H, br m, (CH₂)₄ + OH), 3.09
(2H, d, J 6.1 Hz, CH₂Ar), 3.80 (3H, s, OMe), 4.74 (1H, br, d, OCHCH₂),
5.06 (1H, t, J 6.1Hz, CHOH), 6.8-7.2 (5H, m, ArH ortho to OMe + 2xArH
meta to OMe + pyridine H₃, H₄), 7.56 (1H, m, pyridine H₅) and 8.47 (1H,
dm, J 4.5Hz, pyridine H₆); m/z 313 (M⁺, 5%), 153 (16), 152 (90), 151 (53),
93 (100), 80 (17), and 41 (14).

c) (±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]
pyrimidine

From 4-methylpyrimidine (2.15g, 23.6mmol), LDA (1.0 equiv), and
Intermediate 1 (5.12g, 23.0mmol). The crude product was subjected to
chromatography (SiO₂; Et₂O) to afford the title compound (3.83g) as an
amber oil. (HCl salt m.p. 211-213°C) (HCl salt Found: C, 62.24; H, 6.68;
N, 8.06. C₁₈H₂₃N₂O₃ requires C, 61.44; H, 6.87; N, 7.96%); δ_H (CDCl₃)
1.5-2.1 (8H, br m, (CH₂)₄), 3.10 (2H, d, J 6.5 Hz, CH₂Ar), 3.80 (3H, s,
OMe), 4.15 (1H, br, s OH), 4.74 (1H, br, m, OCHCH₂), 5.10 (1H, t, J
6.5Hz, CHOH), 6.75-6.9 (3H, m, ArH ortho to OMe + 2xArH meta to OMe),
7.09 (1H, dd, J 4.9Hz, pyrimidine H₅), 8.53 (1H, d, J 4.9Hz, pyrimidine H₆),
and 9.07 (1H, d, J 4.0Hz, pyrimidine H₂); m/z 314 (M⁺, 16%), 296 (19),
228 (23), 227 (75), 166 (18), 153 (22), 152 (20), 151 (16), 94 (100), and 41
(26).

EXAMPLE 2

a) (±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]
pyridazine

n-Butyllithium (1.6M in hexanes) (9.5ml, 6.0mmol) was added dropwise to
a solution of methylpyridazine (0.47g, 5.0mmol) in THF (25ml) at -70°C.
The reaction mixture was allowed to stir at this temperature for 0.5h then a
solution of Intermediate 1 (1.1g, 5.0mmol) in THF (20ml) was added. The
mixture was allowed to warm to RT then partitioned between
dichloromethane (25ml) and saturated sodium hydrogen carbonate

solution (25ml). The organic phase was separated, dried (MgSO₄), and concentrated in vacuo to afford the title compound.

5 The following compounds were prepared in a similar manner to the compound of Example 2a.

b) (±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]pyridine

10 From 4-methylpyridine (3.00g, 32.1mmol), *n*-butyllithium (32.1mmol), and Intermediate 1 (6.82g, 31.0mmol). The crude product was subjected to chromatography [SiO₂; EtOAc-hexane, 3:2 (500ml) to 4:1 (1000ml) then EtOAc-methanol, 9:1 (1500ml)] to afford the title compound (9.68g) as fine white needles m.p. 97-101°C (from toluene). δ H (CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 2.45(1H, br, s, CHOH), 2.96 (2H, d, \downarrow 6.5 Hz, CH₂ pyridine),
15 3.80 (3H, s, OMe), 4.70 (1H, br, m, OCHCH₂), 4.81 (1H, t, \downarrow 6.5Hz, CHOH), 6.76(3H, s, ArH *ortho* to OMe + 2xArH *meta* to OMe), 7.00 (2H, dm, \downarrow 4.5Hz, pyridine H₃, H₅), and 8.33 (2H, dm, \downarrow 4.5Hz, pyridine H₂, H₆).

20 c) (±)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]pyrazine

From methylpyrazine (0.94g, 11mmol), *n*-butyllithium (1.6M; 6.9ml, 11mmol), and Intermediate 1 (2.2g, 10mmol) to afford the title compound as a yellowish oil.

25 d) (±)-3-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]-2-methoxypyrazine

From 2-methoxy-3-methylpyrazine (1.76ml, 15mmol), Intermediate 1 (3.3g, 15mmol) and *n*-butyllithium (10.62ml, 17mmol). Chromatography (SiO₂; EtOAc) afforded the title compound (4.473g).

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EXAMPLE 3

a) 3-Amino-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine

35 A solution of Intermediate 4 (2.178g) in THF (50ml) was hydrogenated over Pd/C (10%; 20mg) at RT. The reaction mixture was filtered through Celite[®] and the filtrate concentrated in vacuo. The residue was recrystallised from Et₂O to afford the title compound (1.95g) as a white solid m.p. 108-110.5°C. (Found: C, 72.55; H, 7.66; N, 8.82. C₁₉H₂₄N₂O₂ requires C, 73.04; H, 7.74; N, 8.97%); δ H (CDCl₃) 1.5-2.0

(8H, br m, (CH₂)₄), 2.74-2.85 (4H, br, m, CH₂CH₂Ar), 3.4 (2H, br m, NH₂), 3.79 (3H, s, OMe), 4.64 (1H, br, m, OCH), 6.61 (1H, d, J 2.0 Hz, ArH ortho to cyclopentyloxy), 6.68 (1H, dd, J 8.1, 2.0 Hz, ArH para to cyclopentyloxy), 6.78 (1H, d, J 8.1 Hz, ArH ortho to OMe), 6.85 (1H, d, J 5.1 Hz, pyridine H₅), 7.90 (1H, d, J 5.1 Hz, pyridine H₆), and 7.94 (1H, s, pyridine H₂); m/z 312 (M⁺, 51%), 244 (78), 243 (42), 205 (27), 138 (40), 137 (100), 122 (24), 109 (35), 108 (100), 107 (24), and 41 (24).

The following compounds were prepared in a similar manner to the compound of Exmple 3a.

b) (±)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-pyridyl)-propanenitrile

From Intermediate 3a) (800mg) in methanol (100ml) to afford the title compound (756mg) as a yellow solid: δ_H (CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 3.21 (2H, d, J 7.9 Hz, CH₂CHCN), 3.78 (3H, s, OMe), 4.14 (1H, t, J 7.9 Hz, CH₂CHCN), 4.70 (1H, br m, OCH), 6.6-6.75 (3H, m) and 7.15-7.3 (2H, m) (C₆H₃ + pyridine H₃, H₄), 7.60 (1H ca. dt, J ca. 7.5, 2 Hz, pyridine H₅), 8.56 (1H, dm, J ca. 5 Hz, pyridine H₆); m/z 322 (M⁺, 12%), 296 (15), 254 (30), 228 (10), 138 (18), 137 (100), 79 (10), and 41 (10).

c) (±)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-pyridyl)-propanenitrile

From Intermediate 3 b) (500mg) in methanol (15ml) to afford the title compound (420mg) as a colourless oil; δ_H (CDCl₃) 1.6-2.0 (8H, br m, (CH₂)₄), 3.07 (2H, d, J 7.1 Hz, CH₂CHCN), 3.76 (3H, s, OMe), 3.99 (1H, t, J 7.1 Hz, CH₂CHCN), 4.70 (1H, br m, OCH), 6.5-6.75 (3H, m) and 7.2-7.45 (2H, m) (2xArH meta to OMe + ArH ortho to OMe + pyridine H₄, H₅), and 8.35-8.55 (2H, m, pyridine H₂, H₆); m/z 322 (M⁺, 22%), 254 (51), 205 (38), 138 (76), 137 (100), 122 (34), 118 (16), 94 (16), 85 (16), 65 (15), and 41 (38).

d) (±)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)-propanenitrile

From Intermediate 3 c) (800mg) in methanol (100ml) to afford the title compound (712mg) as a yellow oil; δ_H (CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 3.08 (2H, d, J 7.1 Hz, CH₂CHCN), 3.79 (3H, s, OMe), 3.96 (1H, t, CH₂CHCN), 4.65 (1H, br m, OCH), 6.5-6.8 (3H, m, 2xArH meta to OMe

+ ArH ortho to OMe), 7.10 (2H, dd, Δ 4.5, 1.8Hz, pyridine H₃, H₅), and 8.45 (2H, dd, Δ 4.5, 1.8 Hz pyridine H₂, H₆); m/z 322 (M⁺, 5%), 254 (13), 229 (10), 138 (13), 137 (100), 85 (15), and 41 (12).

5 e) 2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine

From Intermediate 5 b) (0.72g) to afford the title compound (0.68g) as a pale yellow oil. (Found: C, 76.23; H, 7.79; N, 4.52. C₁₉H₂₃NO₂ requires C, 76.74; H, 7.80; N, 4.71%); δ H (CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 2.9-3.1 (4H, m, CH₂CH₂Ar), 3.81 (3H, s, OMe), 4.70 (1H, br, m, OCH), 6.65-6.8 (3H, m) and 7.0-7.15 (2H, m) (pyridine H₃, H₄ and C₆ H₃), 7.55 (1H, dt, Δ 7.6, 1.8Hz, pyridine H₅) and 8.56 (1H, dm Δ ~5Hz, pyridine H₆); m/z 297 (M⁺, 27%), 229 (60), 228 (51), 214 (39), 138 (13), 137 (100), 106 (17), 94 (12), 93 (53), and 41 (20).

15 i) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine

From Intermediate 6 b) (700mg) in methanol (100ml) containing a few drops of triethylamine to afford the title compound (685mg) (Found: C, 76.55; H, 7.88; N, 4.89. C₁₉H₂₃NO₂ requires C, 76.48; H, 8.10; N, 4.69%).

20

g) 2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]pyrazine

From Intermediate 6 c) (700mg) in methanol (100ml) to afford the title compound (680mg) as yellow crystals. (Found: C, 72.36; H, 7.47; N, 9.17. C₁₈H₂₂N₂O₂ requires C, 72.46; H, 7.43; N, 9.39%); δ H (CDCl₃) 1.4-2.0 (8H, br m, (CH₂)₄), 2.95-3.1 (4H, m, CH₂CH₂Ar), 3.78 (3H, s, OMe), 4.67 (1H, br, m, OCH), 5.5-6.7 (3H, m, 2xArH meta to OMe + ArH ortho to OMe) and 8.3-8.5 (3H, m, pyrazine H₃, H₅, H₆).

25

h) 3-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-2-methoxy-pyrazine

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From Intermediate 5d (770mg) in methanol (100ml) to afford the title compound (700mg) as a colourless oil (Found: C, 69.51; H, 7.39; N, 3.45. C₁₉H₂₄N₂O₃ requires C, 69.49; H, 7.37; N, 8.53%); δ H (CDCl₃) 1.4-2.0 (8H, br m, (CH₂)₄), 2.9-3.1 (4H, m, CH₂CH₂Ar), 3.78 (3H, s, OMe), 3.92 (3H, s, OMe), 4.70 (1H, br, m, OCH), 6.72 (3H, s, 2xArH meta to OMe + ArH ortho to OMe), 7.87 (1H, d, Δ 2.8Hz) and 7.98 (1H, d, Δ 2.8Hz), (pyrazine H₅, H₆); m/z 338 (M⁺, 31%), 271 (11), 270 (63), 205 (40), 137 (100), and 122 (9).

35

i) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)propyl]pyridine

From a mixture of the three stereoisomers described in Intermediate 5c (0.9g). Chromatography (SiO₂; EtOAc) afforded the title compound (0.696g) as a clear oil. (Found C, 76.88; H, 8.07; N, 4.36. C₂₀H₂₅NO₂ requires C, 77.14; H, 8.09; N, 4.50). δ_H (CDCl₃) 1.26 (3H, ca. d, \downarrow 6.3Hz CHMe), 1.5-2.0 (8H, br m, (CH₂)₄), 2.7-2.9 (3H, m, MeCHCH₂), 3.78 (3H, s, OMe), 6.55-6.8 (3H, m, C₆H₃), 6.89 (2H, dm, \downarrow ca 4.5Hz, pyridine H₃, H₅), and 8.36 (2H, dm, \downarrow ca 4.5Hz, pyridine H₂ H₆); m/z (EI) 311 (M⁺, 29%), 243 (100), 242 (23), 219 (58), 151 (86), and 91 (18).

j) (±)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-naphthyl)propanenitrile

From Intermediate 3d (1.5g). Filtration through celite followed by concentration in vacuo afforded the title compound (0.351g) as a white solid. m.p. 134-135°C. (Found C, 80.852; H, 6.808; N, 3.822. C₂₅H₂₃NO₂ requires C, 80.832; H, 6.783; N, 3.77%). m/z 371 (18%), 137 (100), and 205 (96).

20 EXAMPLE 4a) 3-Benzamido-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine

Benzoyl chloride (0.13ml, 1.0 mmol) was added to a solution of the compound of Example 3 a) (263mg, 0.88mmol) in pyridine (10ml) and the reaction mixture allowed to stir at RT for 18h. The mixture was concentrated in vacuo and the residue was subjected to chromatography (SiO₂; EtOAc) to afford the title compound (237mg) as a white foam m.p. 50-51°C (Found: C, 74.44; H, 6.79; N, 6.69. C₂₆H₂₈N₂O₃ requires C, 74.97; H, 6.77; N, 6.77%); δ_H (CDCl₃) 1.5-1.9 (8H, br m, (CH₂)₄), 2.90 (4H, br, s, CH₂CH₂Ar), 3.78 (3H, s, OMe), 4.48 (1H, br, m, OCH), 6.43 (1H, d, \downarrow 2.0Hz ArH ortho to cyclopentyloxy), 6.57 (1H, dd, \downarrow 8.1, 2.0Hz, ArH para to cyclopentyloxy), 6.74 (1H, d, \downarrow 8.1Hz, ArH ortho to OMe), 6.93 (1H, br s, NHCO), 7.22 (1H, d, \downarrow 5.0Hz, pyridine H₅), 7.4-7.65 (5H, m, C₆H₅), 8.42 (1H, d, \downarrow 5.0 Hz, pyridine H₆) and 8.81 (1H, s, pyridine H₂); m/z 416 (M⁺, 14%), 349 (22), 348 (100), 347 (26), 212 (17), 199 (18), 137 (93), 105 (90), and 77 (38).

The following compounds were prepared in a manner similar to the compound of Example 4a.

b) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-3-methylamido-pyridine

5

From the compound of Example 3 a) (309mg, 1.0mmol) and acetyl chloride (0.1ml, 1.4mmol) to afford the title compound (276mg) as white crystals. δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 1.96 (3H, s, $NHCOMe$), 2.85 (4H, s, CH_2CH_2Ar), 3.82 (3H, s, OMe), 4.59 (1H, br, s, OCH), 6.18 (1H, br s, $NHCOMe$), 6.46 (1H, d, \downarrow 2.0Hz, ArH ortho to cyclopentyloxy), 6.63 (1H, dd, \downarrow 8.1, 2.0Hz, ArH para to cyclopentyloxy), 6.81 (1H, d, \downarrow 8.1Hz, ArH ortho to OMe), 7.15 (1H, d, \downarrow 4.9Hz, pyridine H_5), 8.36 (1H, br d, \downarrow ca 4.6Hz, pyridine H_6), and 8.70 (1H, br s, pyridine H_2); m/z 354 (M^+ , 8%), 286 (50), 285 (16), 151 (27), 150 (47), 138 (17), 137 (100), 122 (10), 119 (11), 43 (17), and 41 (17).

15

c) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-3-isobutylamido-pyridine

20

From the compound of Example 3 a) (450mg, 1.5mmol) and isobutyryl chloride (0.22ml, 2.1mmol) to afford the title compound (310mg) as a white solid m.p. 100-101.5°C (Found: C, 72.01; H, 7.90; N, 7.26. $C_{23}H_{30}N_2O_3$ requires C, 72.22; H, 7.90; N, 7.32%); δ_H ($CDCl_3$) 1.15 (6H, d, \downarrow 6.9Hz, $CHMe_2$), 1.1-1.8 (8H, br m, $(CH_2)_4$), 2.26 (1H, m, $CHMe_2$), 2.84 (4H, s, CH_2CH_2Ar), 3.81 (3H, s, OMe), 4.58 (1H, br, m, OCH), 6.22 (1H, br s, $NHCO$), 6.44 (1H, d, \downarrow 2.0Hz ArH ortho to cyclopentyloxy), 6.62 (1H, dd, \downarrow 8.1, 2.0Hz, ArH para to cyclopentyloxy), 6.80 (1H, d, \downarrow 8.1Hz, ArH ortho to OMe), 7.13 (1H, d, \downarrow 5.0Hz, pyridine H_5), 8.35 (1H, d, \downarrow 5.0 Hz, pyridine H_6), and 8.71 (1H, br s, pyridine H_2); m/z 382 (M^+ , 21%), 315 (19), 314 (89), 313 (39), 178 (12), 137 (100), 43 (32), and 41 (41).

25

30

d) 3-(3-Benzylureido)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine

35

From the compound of Example 3 a) (399mg, 1.3mmol) and benzylisocyanate (0.23ml, 1.8mmol) to afford the title compound (477mg) as a white solid m.p. 152-154°C (Found: C, 72.76; H, 7.04; N, 9.36. $C_{27}H_{31}N_3O_3$ requires C, 72.78; H, 7.01; N, 9.43%); δ_H ($CDCl_3$) 1.5-1.9 (8H, br m, $(CH_2)_4$), 2.84 (4H, m, CH_2CH_2Ar), 3.76 (3H, s, OMe), 4.36 (2H, d, \downarrow 5.7Hz, $NHCH_2$), 4.62 (1H, m, $NHCH_2$), 4.71 (1H, br m, OCH), 5.59

(1H, br s, NH Ar), 6.52 (1H, d, \downarrow 2.1Hz ArH ortho to cyclopentyloxy), 6.60 (1H, dd, \downarrow 8.2, 2.1Hz, ArH para to cyclopentyloxy), 6.74 (1H, d, \downarrow 8.2Hz, ArH ortho to OMe), 7.10 (1H, d, \downarrow 5.0Hz, pyridine H₅), 7.2-7.3 (5H, m, C₆H₅), 8.31 (1H, d, \downarrow 5.0 Hz, pyridine H₆), and 8.62 (1H, s, pyridine H₂).

5

e) N-[4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-3-pyridyl]phenylsulphonamide

From the compound of Example 31 (0.416g, 1.3mmol) and benzene-sulfonylchloride (0.22ml, 1.6mmol). Chromatography (SiO₂; Et₂O) afforded the title compound (0.460g) as a yellow solid. m.p. 183.9-185.3. Found: C, 66.22; H, 9.76; N, 5.76. C₂₅H₂₈N₂O₄S requires C, 63.81; H, 6.42; N, 5.95%. δ _H (CDCl₃) 1.5-1.9 (8H, br m, (CH₂)₄), 2.73 (4H, s, ArCH₂CH₂ pyridine), 3.85 (3H, s, OMe), 4.62 (1H, br m, OCH₂), 5.7 (1H, br s NH), 6.43 (1H, d, \downarrow 2.0Hz ArH ortho to cyclopentyloxy), 6.59 (1H, dd, \downarrow 8.2, 2.0Hz, ArH para to cyclopentyloxy), 6.82 (1H, d, \downarrow 8.2Hz, ArH ortho to OMe), 7.08 (1H, d, \downarrow 4.9Hz, pyridine H₅), 7.45-7.5 (2H, m, ArH meta to SO₂NH), 7.55-7.6 (1H, m, ArH para to SO₂NH), 7.65-7.7 (2H, m, ArH ortho to SO₂NH), 8.20 (1H, ca s, pyridine H₂), and 8.6 (1H, d, \downarrow 4.9Hz, pyridine H₆); m/z (EI) 453 (M^{++} 1, 30%), 452 (M^+ , 98), 385 (24), 384 (100), 383 (16), 243 (14), and 137 (40).

20

FORMULATION EXAMPLES

The compounds of the invention may be formulated for pharmaceutical use in a number of forms using any suitable excipients. Thus, for example, for oral use the compounds of the invention such as the compounds of the Examples may be formulated as a solid dosage form, by mixing an appropriate weight of compound (for example 50mg) with maize starch (50-99%w/w), anhydrous colloidal silica (0-10%w/w) and organic or inorganic acid (up to 1%w/w), to fill capsules of an appropriate size, e.g. white opaque hard gelatine capsules size 3. If desired the same mixture may be compressed into tablets.

The activity and selectivity of compounds according to the invention was demonstrated in the following tests. In these tests the abbreviation FMLP represents the peptide N-formyl-met-leu-phe.

35

Isolated Enzyme

The potency and selectivity of the compounds of the invention was determined using distinct PDE isoenzymes as follows:

- i. PDE I, rabbit heart
- ii. PDE II, rabbit heart
- iii. PDE III, rabbit heart, Jurkat cells
- iv. PDE IV, HL60 cells, rabbit brain, rabbit kidney and human recombinant PDE IV
- v. PDE V, rabbit lung, guinea pig lung

A gene encoding human PDE IV has been cloned from human monocytes (Livi, *et al.*, 1990. *Molecular and Cellular Biology*, 10, 2678). Using similar procedures we have cloned human PDE IV genes from a number of sources including eosinophils, neutrophils, lymphocytes, monocytes, brain and neuronal tissues. These genes have been transfected into yeast using an inducible vector and various recombinant proteins have been expressed which have the biochemical characteristics of PDE IV (Beavo and Reifsnnyder, 1990, *TIPS*, 11, 150). These recombinant enzymes, particularly the human eosinophil recombinant PDE IV, have been used as the basis of a screen for potent, selective PDE IV inhibitors.

The enzymes were purified to isoenzyme homogeneity using standard chromatographic techniques.

Phosphodiesterase activity was assayed as follows. The reaction was conducted in 150µl of standard mixture containing (final concentrations): 50mM 2-[[Tris(hydroxymethyl)methyl]amino]-1-ethane-sulphonic acid (TES)-NaOH buffer (pH 7.5), 10mM MgCl₂, 0.1µM [³H]-cAMP and vehicle or various concentrations of the test compounds. The reaction was initiated by addition of enzyme and conducted at 30°C for between 5 to 30 mins. The reaction was terminated by addition of 50µl 2% trifluoroacetic acid containing [¹⁴C]-5'AMP for determining recovery of the product. An aliquot of the sample was then applied to a column of neutral alumina and the [³H]-cAMP eluted with 10ml 0.1 TES-NaOH buffer (pH8). The [³H]-5'-AMP product was eluted with 2ml 2M NaOH into a scintillation vial containing 10ml of scintillation cocktail. Recovery of [³H]-5'AMP was determined using the [¹⁴C]-5'AMP and all assays were conducted in the linear range of the reaction.

Compounds according to the invention such as compounds of the Examples herein cause a concentration-dependent inhibition of recombinant PDE IV at 0.1 - 1000nM with little or no activity against PDE I, II, III or V at concentrations up to 100µM.

2. The Elevation of cAMP In Leukocytes

The effect of compounds of the invention on intracellular cAMP was investigated using human neutrophils or guinea pig eosinophils. Human neutrophils were separated from peripheral blood, incubated with dihydrocytochalasin B and the test compound for 10 min and then stimulated with FMLP. Guinea pig eosinophils were harvested by peritoneal lavage of animals previously treated with intra-peritoneal injections of human serum. Eosinophils were separated from the peritoneal exudate and incubated with isoprenaline and test compound. With both cell types, suspensions were centrifuged at the end of the incubation, the cell pellets were resuspended in buffer and boiled for 10 min prior to measurement of cAMP by specific radioimmunoassay (DuPont).

The most potent compounds according to the Examples induced a concentration -dependent elevation of cAMP in neutrophils and/or eosinophils at concentrations of 0.1nM to 1µM.

3. Suppression of Leukocyte Function

Compounds of the invention were investigated for their effects on superoxide generation, chemotaxis and adhesion of neutrophils and eosinophils. Isolated leukocytes were incubated with dihydrocytochalasin B for superoxide generation only and test compound prior to stimulation with FMLP. The most potent compounds of the Examples caused a concentration-dependent inhibition of superoxide generation, chemotaxis and adhesion at concentrations of 0.1nM to 1µM.

Lipopolysaccharide (LPS)-induced synthesis of tumour necrosis factor (TNF) by human peripheral blood monocytes (PBM) is inhibited by compounds of the Examples at concentrations of 0.01nM to 10µM.

4. Relaxation of Constricted Airway Smooth Muscle in vitro

The effects of compounds of the invention on guinea-pig isolated tracheal smooth muscle were investigated. Isolated tracheal rings were suspended in organ baths and immersed in oxygenated Krebs' solution. The smooth muscle was contracted with sub-maximal concentrations of histamine or carbachol prior to the addition of increasing concentrations of test compound to the organ baths. The most potent compounds of the Examples caused a concentration-dependent reversal of both histamine and carbachol-induced contractions at concentrations of 1nM to 100µM. The compounds were generally more potent in reversing histamine-induced tone than carbachol-induced tone.

5. Effects on Cardiac Muscle in vitro

Compounds of the invention have been tested for their effects on isolated cardiac muscle. Right atrial and papillary muscles were dissected out from the hearts of guinea pigs and suspended in organ baths for measuring the rate (chronotropic) of spontaneously beating atria and force (inotropic) of the electrically stimulated papillary muscle. In these preparations, selective PDE IV inhibitors such as rolipram do not have any direct effects whereas selective PDE III inhibitors such as milrinone have positive chronotropic and inotropic effects. The non-specific PDE inhibitor theophylline, which is used in asthma as a bronchodilator, also causes significant cardiovascular changes such as tachycardia. Selective PDE IV inhibitors have advantage over theophylline, therefore, through reduced cardiovascular side effects. The most potent and selective compounds of the Examples had no direct effects on the atrial and papillary muscles in vitro at concentrations up to 10µM but in combination with PDE III inhibitors, these inhibitors showed an enhancement of chronotropic and inotropic activity, typical of selective type IV inhibitors.

6. Anti-Inflammatory Activity in vivo

Interleukin-5 (IL-5)-induced pleural eosinophilia in the rat (*Lisie, et al*, 1993, *Br.J. Pharmacol.* 108, 230p) is inhibited by compounds of the Examples given orally at doses of 0.0001 to 10.0mg/kg. The most

potent compounds cause a dose-dependent reduction in migrating eosinophils with ED₅₀s of 0.003 to 0.03mg/kg p.o.

5 Compounds of the invention also reduce the inflammatory responses induced in rats by platelet activating factor (PAF).

7. **Anti-allergic Activity in vivo**

10 Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitised guinea pigs. Guinea pigs were initially sensitised to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminium hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later and at 15 six weeks, animals were challenged with aerosolised ovalbumin whilst under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also 20 removed for histological examination for inflammatory damage. Administration of compounds of the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilla and the accumulation of other inflammatory leukocytes. There was also less 25 inflammatory damage in the lungs of animals treated with compounds of the Examples.

8. **Effects on Pulmonary Dynamics**

30 Compounds of the invention (0.001-10mg/kg by oral or other route of administration) reduce the allergic bronchoconstriction caused by antigen in sensitized guinea pigs.

35 Compounds of the invention have been tested for their effects on ozone-induced hyperreactivity of the airways of guinea pigs. Following the inhalation of ozone, guinea pigs become very much more sensitive to the bronchoconstrictor effects of inhaled histamine than naive animals (Yeadon *et al.* 1992, *Pulmonary Pharm.* 5, 39). There is a pronounced shift to the left (10-30 fold) of the dose

response curve to histamine and a highly significant increase in the maximum increase in pulmonary resistance. Compounds of the Examples administered 1h prior to ozone by the intraperitoneal or oral (0.001-10mg/kg) route caused a dose-dependent inhibition of ozone-induced hyperreactivity.

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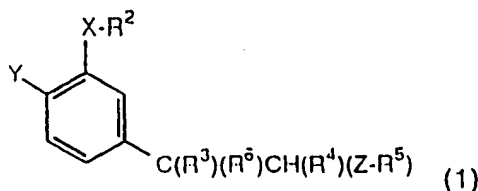
9. Adverse Effects

In general, in our tests above, compounds of the invention have had no observed toxic effects when administered to animals at the doses shown.

10

CLAIMS

1. A compound of formula (1)



wherein

Y is a halogen atom or a group -OR¹, where R¹ is an optionally substituted alkyl group;

X is -O-, -S-, or -N(R⁷)-, where R⁷ is a hydrogen atom or an alkyl group;

R² is an optionally substituted cycloalkyl or cycloalkenyl group;

R³ and R⁴, which may be the same or different, is each a hydrogen atom or an alkyl, -CO₂R⁸ (where R⁸ is a hydrogen atom or an optionally substituted alkyl, aryl, or aralkyl group), -CONR⁹R¹⁰ (where R⁹ and R¹⁰ which may be the same or different is each a hydrogen atom or an alkyl, aryl or aralkyl group), -CSNR⁹R¹⁰, -CN, or -CH₂CN group;

Z is -(CH₂)_n- where n is zero or an integer 1, 2 or 3;

R⁵ is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

R⁶ is a hydrogen atom or a hydroxyl group;

and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

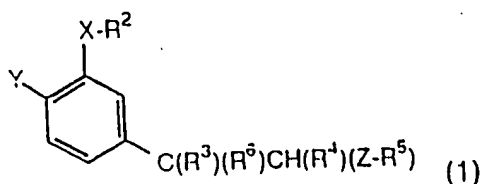
2. A compound according to Claim 1 wherein Y is a group -OR¹.
3. A compound according to Claim 2, where R¹ is an optionally substituted straight or branched C₁₋₃ alkyl group.
4. A compound according to Claim 3 wherein R¹ is a -CH₃ group.

5. A compound according to any of Claims 1 to 4, wherein X is -O-.
6. A compound according to any of Claims 1 to 5 wherein R² is a cyclopentyl group.
- 5 7. A compound according to any of the preceding claims wherein Z is a -(CH₂)_n- group where n is zero or an integer 1 or 2.
8. A compound according to Claim 7 wherein Z is a -(CH₂)_n- group where n is zero.
- 10 9. A compound according to any of Claims 1 to 8 wherein R³ is a hydrogen atom or a -CH₃ group.
10. A compound according to Claim 9 where R³ is a hydrogen atom.
- 15 11. A compound according to any of Claims 1 to 10 wherein R⁴ is a hydrogen atom or an optionally substituted C₁₋₃ alkyl or -CN group.
12. A compound according to Claim 11 wherein R⁴ is a hydrogen atom or a -CN group.
- 20 13. A compound according to any of the preceding claims wherein R⁶ is a hydrogen atom.
- 25 14. A compound according to Claims 1 to 13 wherein R⁵ is an optionally substituted C₆₋₁₂ aryl or C₃₋₉ heteroaryl group containing one, two or three heteroatoms selected from -O-, -S- or -N- atoms.
- 30 15. A compound according to Claim 14 wherein R⁵ is an optionally substituted phenyl, pyridyl or pyrimidinyl group.
16. A compound according to Claim 15 where R⁵ is a phenyl or a 2- or 3- monosubstituted or 2,6-disubstituted phenyl group.

17. A compound according to Claim 15 where R⁵ is a 2-, 3- or 4-pyridyl group or a 3,5-disubstituted- or 3-monosubstituted-4-pyridyl group.
- 5 18. A compound according to any of Claims 14 to 17 wherein the aryl or heteroaryl group is substituted by one or more substituents R¹¹ wherein R¹¹ is an atom or group R¹² or -Alk¹(R¹²)_m wherein R¹² is a halogen atom, or an amino (-NH₂), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, formyl [HC(O)-], carboxyl (-CO₂H), esterified carboxyl, thiol (-SH), substituted thiol, 10 -C(O)R^{8a}, (where R^{8a} is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group), -SO₃H, -SO₂R^{8a}, -SO₂N(R^{8a})(R^{9a}), (where R^{9a} is as defined for R^{8a} and may be the same as or different to R^{8a}), -CON(R^{8a})(R^{9a}), -NHSO₂R^{8a}, -N[SO₂R^{8a}]₂, -NHSO₂N(R^{8a})(R^{9a}), -NHC(O)R^{8a}, or -NHC(O)OR^{8a} group; Alk¹ is a 15 straight or branched C₁₋₆alkylene, C₂₋₆alkenylene, or C₂₋₆alkynylene chain optionally interrupted by one, two, or three -O-, or -S- atoms or -S(O)p-, [where p is an integer 1 or 2] or -N(R⁷)- (where R⁷ is a hydrogen atom or an optionally substituted alkyl group) groups; and m is zero or an integer 1, 2 or 3.
- 20 19. A compound according to Claim 18 wherein R¹¹ is a halogen atom or a nitro, amino, alkoxy, haloalkyl, hydroxy, -NHCOR^{8a}, -NHCONHR^{8a}, or -NHSO₂R^{8a} group.
- 25 20. A compound which is:
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;
(±)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)propanenitrile;
3-Benzamido-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;
N-(4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-3-pyridyl)phenyl-
30 sulphonamide;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-3,5-dichloropyridine;
3-Amino-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine;
4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]-3-
isobutylamidopyridine;
35 or

3-(3-Benzylureido)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine; and the salts, solvates, hydrates and N-oxides thereof.

21. A pharmaceutical composition comprising a compound of formula (1):



wherein

Y is a halogen atom or a group $-OR^1$, where R^1 is an optionally substituted alkyl group;

X is $-O-$, $-S-$, or $-N(R^7)-$, where R^7 is a hydrogen atom or an alkyl group;

R^2 is an optionally substituted cycloalkyl or cycloalkenyl group;

R^3 and R^4 , which may be the same or different, is each a hydrogen atom or an alkyl, $-CO_2R^8$ (where R^8 is a hydrogen atom or an optionally substituted alkyl, aryl, or aralkyl group), $-CONR^9R^{10}$ (where R^9 and R^{10} which may be the same or different is each a hydrogen atom or an alkyl, aryl or aralkyl group), $-CSNR^9R^{10}$, $-CN$, or $-CH_2CN$ group;

Z is $-(CH_2)_n-$ where n is zero or an integer 1, 2 or 3;

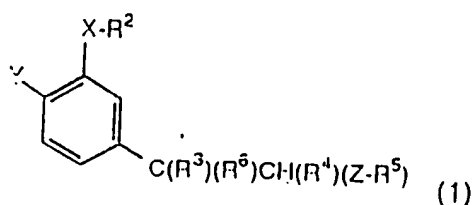
R^5 is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

R^6 is a hydrogen atom or a hydroxyl group;

and the salts, solvates, hydrates, prodrugs and N-oxides thereof, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

30

22. A process for the preparation of a compound of formula (1)



wherein

Y is a halogen atom or a group $-OR^1$, where R^1 is an optionally substituted alkyl group;

X is $-O-$, $-S-$, or $-N(R^7)-$, where R^7 is a hydrogen atom or an alkyl group;

R^2 is an optionally substituted cycloalkyl or cycloalkenyl group;

R^3 and R^4 , which may be the same or different, is each a hydrogen atom or an alkyl, $-CO_2R^8$ (where R^8 is a hydrogen atom or an optionally substituted alkyl, aryl, or aralkyl group), $-CONR^9R^{10}$ (where R^9 and R^{10} which may be the same or different is each a hydrogen atom or an alkyl, aryl or aralkyl group), $-CSNR^9R^{10}$, $-CN$, or $-CH_2CN$ group;

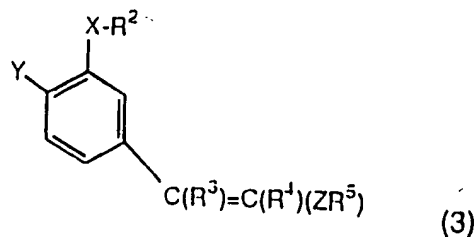
Z is $-(CH_2)_n-$ where n is zero or an integer 1, 2 or 3;

R^5 is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

R^6 is a hydrogen atom or a hydroxyl group;

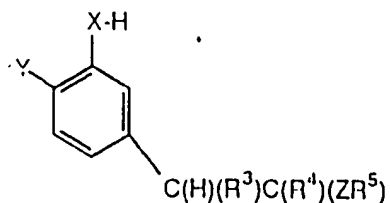
and the salts, solvates, hydrates, prodrugs and N-oxides thereof, which comprises in a final step:

a) hydrogenating a compound of formula (3)



wherein Y, X, R^2 , R^3 , R^4 , Z and R^5 are as described for formula (1);

- b) alkylating a compound of formula (7)

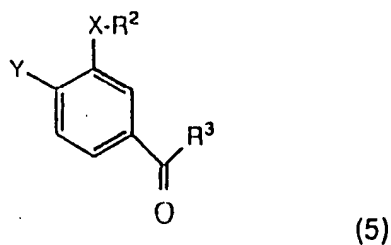


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wherein Y, X, R^3 , R^4 , Z and R^5 are as described for formula (1) with a halide $\text{R}^2 \text{ Hal}$ or an alcohol R^2OH ;

- c) in the preparation of a compound of formula (1) where R^6 is -OH reacting a ketone or aldehyde of formula (5)

10



(5)

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with an organometallic reagent $\text{R}^4\text{R}^5\text{ZCHM}$ (where M is a metal atom), or

- d) interconverting a compound of formula (1) to another compound of formula (1).

20

INTERNATIONAL SEARCH REPORT

Inter- national Application No
PCT/GB 94/00453

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C43/235 A01N43/40 C07D213/30 C07D237/08 C07D241/12
A01N43/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category* Citation of document, with indication, where appropriate, of the relevant passages

Relevant to claim No.

X

EP,A,0 470 805 (AMERICAN HOME PRODUCTS CORPORATION) 12 February 1992
see examples 4,5

A

WO,A,92 06963 (BYK GULDEN LOMBERG CHEMISCHE FABRIK) 30 April 1992

A

WO,A,91 15451 (SMITH-KLINE BEECHAM CORPORATION) 17 October 1991

1-16,21

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Date of the actual completion of the international search

6 May 1994

Date of mailing of the international search report

27.05.94

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 94/00453

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0470805	12-02-92	US-A- 5124455	23-06-92
		AU-B- 640251	19-08-93
		AU-A- 8162391	13-02-92
		CA-A- 2048518	09-02-92
		CN-A- 1058771	19-02-92
		GB-A- 2246777	12-02-92
		HU-B- 207289	29-03-93
		JP-A- 4253945	09-09-92
WO-A-9206963	30-04-92	AU-A- 8722991	20-05-92
		CA-A- 2094127	17-04-92
		EP-A- 0553174	04-08-93
		JP-T- 6501941	03-03-94
WO-A-9115451	17-10-91	AU-A- 7670991	30-10-91
		EP-A- 0523138	20-01-93
		JP-T- 6500071	06-01-94